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Weaning of non COPD patients at high-risk of extubation failure assessed by lung ultrasound: the WIN IN WEAN multicentre randomised controlled trial

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Abstract

Background Postextubation respiratory failure (PRF) frequently complicates weaning from mechanical ventilation and may increase morbidity/mortality. Noninvasive ventilation (NIV) alternating with high-flow nasal oxygen (HFNO) may prevent PRF.

Methods Ventilated patients without chronic obstructive pulmonary disease (COPD) and at high-risk of PRF defined as a lung ultrasound score (LUS) ≥ 14 assessed during the spontaneous breathing trial, were included in a French-Chinese randomised controlled trial. PRF was defined by 2 among the following signs: $SpO_2 < 90\%$; Respiratory rate > 30 /min; hypercapnia; haemodynamic and/or neurological disturbances of respiratory origin. In the intervention group, prophylactic NIV alternating with HFNO was administered for 48 h following extubation. In the control group, conventional oxygen was used. Clinicians were informed on the LUS in the intervention group, those in the control group remained blind. The primary outcome was the incidence of PRF 48 h after extubation. Secondary outcomes were incidence of PRF and reintubation at day 7, number of ventilator-free days at day 28, length of ICU stay and mortality at day 28 and 90.

Results Two hundred and forty patients were randomised and 227 analysed (intervention group = 128 and control group = 99). PRF at H48 was reduced in the intervention group compared to the control group: relative risk 0.52 (0.31 to 0.88), $p = 0.01$. The benefit persisted at day 7: relative risk 0.62 (0.44 to 0.96), $p = 0.02$. Weaning failure imposing reconnection to mechanical ventilation was not reduced. In patients who developed PRF and were treated by rescue NIV, reintubation was avoided in 44% of control patients and in 12% of intervention patients ($p = 0.008$). Other secondary outcomes were not different between groups. From a resource utilisation standpoint, prophylactic NIV alternating with HFNO was more demanding and costly than conventional oxygen with rescue NIV to achieve same clinical outcome.

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Conclusions Compared to conventional oxygenation, prophylactic NIV alternating with HFNO significantly reduced postextubation respiratory failure but failed to reduce reintubation rate and mortality in patients without COPD at high risk of extubation failure. Prophylactic NIV alternating with HFNO was as efficient as recue NIV to treat postextubation respiratory failure.

Keywords Weaning, High flow nasal oxygen, Noninvasive ventilation, Lung ultrasound score, Postextubation respiratory failure, Reintubation

Background

After a period of mechanical ventilation, extubation is a key step towards discharge from the intensive care unit (ICU). When the physician considers that the respiratory disease justifying mechanical ventilation has been effectively treated, a spontaneous breathing trial (SBT) is undertaken [1, 2]. If, after 30 min, there is no respiratory distress, the patient is extubated. Extubation failure is defined as the onset of postextubation acute respiratory failure (PRF) requiring rescue NIV and/or reintubation within seven days [3, 4]. Once extubated, 25% of high-risk patients experience PRF and half are reintubated [5]. Reintubation is associated with an increased mortality, an increased incidence of ventilator-associated pneumonia, a prolongation of mechanical ventilation and a longer ICU stay [5–7].

In 2017, international guidelines recommended the use of prophylactic NIV to prevent PRF in patients at high risk of extubation failure [8]. A multicentre randomized controlled trial reported a significant reduction of postextubation reintubation rate with prophylactic NIV alternating with high-flow nasal oxygen (HFNO) compared to HFNO alone [9]. A meta-analysis confirmed that both NIV and HFNO reduced postextubation reintubation in high-risk patients [10]. High-risk criteria classically include age > 65 years, high APACHE II score, body mass index > 30, chronic cardiac or pulmonary disease, long duration of mechanical ventilation, difficult weaning, inability to deal with respiratory secretions, diaphragmatic weakness, and neurological impairment [9, 11–15]. Switching from positive pressure ventilation to spontaneous breathing can result in alveolar derecruitment-induced aeration loss and PRF [16]. Chronic obstructive pulmonary disease (COPD) is the first cause of PRF, and the deterioration of lung aeration following extubation justifies prophylactic NIV [17–19].

Transthoracic lung ultrasound accurately assesses lung aeration loss [20] and a lung ultrasound score (LUS) ≥ 14 has been shown to be predictive of PRF [16]. Using lung ultrasound has the advantage of individualizing the risk of extubation failure. In the WIN IN WEAN randomised controlled trial we aimed to evaluate whether prophylactic use of NIV alternating with HFNO, compared with conventional oxygen, could reduce the incidence of PRF in patients free of COPD whose high risk was personalised by a LUS ≥ 14 at the end of a successful SBT.

Methods

Study design

WIN-IN-WEAN is a multicentre, randomised, placebo-controlled trial, conducted in 9 French and 3 Chinese ICUs (*see* additional file 1). Trial recruitment lasted from March 6, 2014, to May 20, 2018. Follow-up ended on August 31, 2021. The study was registered under trial number NCT02123940. The trial protocol and statistical analysis plan were evaluated and approved by independant reviewers of the French Ministry of Health when the WIN-IN-WEAN study was submitted for funding to the "Programme Hospitalier de Recherche Clinique Regional 2014" (University Hospital of Poitiers, France PHRCI-14-003). To take into consideration data showing that the success or failure of weaning are to be assessed in the first 7 days after extubation [3], an amendment to the protocol was made in october 2015. The trial protocol and CONSORT checklist is available in additional file 2. The WIN-IN-WEAN study was coordinated by the Direction of Clinical Research and Innovation (DRCI) of the Centre Hospitalier Universitaire of Clermont-Ferrand, and overseen by an independent Steering Committee. Data were prospectively collected in a customised Electronic Case Report Form using the web-based application Research Electronic Data Capture (*see* additional file 2, pages 16–17 and 85). Accuracy of the data recorded were regularly monitored by research assistants on site in France and by electronical connection in China. Face masks, oxygen blenders, heated humidifiers for NIV and HFNO, and cannulas for HFNO were donated by Fisher and Paykel Healthcare Auckland, New Zealand, which had no other involvement in the study. The WIN-IN-WEAN protocol is available in French (pages 2–71) and English (page 72–89) in additional file 2. In France, the study protocol was approved by the Ethics Committee Sud-Est VI (Clermont-Ferrand, France) on Feb 02, 2014; in China, the protocol was approved by the local Ethics Committee of each centre.

Patients

Inclusion criteria

Inclusion criteria were age above 18, mechanical ventilation for more than 48 h, successful 30-min SBT using either T-piece or pressure support ventilation [21], and a LUS ≥ 14 measured at the end of the SBT. Eligibility to SBT was defined according to international conference consensus criteria [22] and undertaken after therapeutic optimisation (*see* additional file pages 13). Before the spontaneous breathing trial, drainage of large pleural effusion, control of fluid overload, fiberoptic suctioning of atelectasis and bacteriological assessment of distal pulmonary sample were systematically performed.

Exclusion criteria

COPD, tracheostomy, tetraplegia, paraplegia above the 8th thoracic segment, unplanned extubation (accidental or self-extubation), do-not-reintubate order at time of inclusion, refusal to participate, inclusion in another interventional study, major protected, pregnancy, and lack of acoustic window. All patients or their relatives provided written informed consent.

Lung ultrasound score and risk for extubation failure

Transthoracic lung ultrasound was performed at the end of the 30-min successful SBT by a senior physician with an expertise in lung ultrasound. Videoslide presentations that were used for providing basic skills in lung ultrasound can be freely downloaded by clicking on the 10 URLs displayed in additional file 3, page 90. As previously recommended [16, 25], 12 regions of interest were examined (*see* additional file 2, pages 8 and 75 and 76). Each was classified in one of the following categories: 0) normal aeration: horizontal A lines with ≤ 2 vertical B lines; 1) moderate aeration loss: multiple spaced B1 lines and/or localized coalescent B2 lines; 2) severe aeration loss: generalized coalescent B2 lines (pulmonary edema); 3) complete aeration loss: lung consolidation with static and/or dynamic air bronchograms. A value (0, 1, 2 or 3) was attributed to each region examined and the LUS was equal to the sum of the 12 regions examined [16]. Score quotation allowed to differentiate focal from ubiquitous B2 lines (moderate versus severe aeration loss) [26–28] (*see* additional file 3, p 90: performance and LU Score, http://links.lww.com/ALN/C155). High individual risk for PRF was defined as a LUS ≥ 14 at the end of the SBT. Selecting a LUS threshold of 14 is issued from our pilot study published in 2012 [16]. In 86 critically ill patients ready to be extubated, the lung ultrasound score best predicting postextubation respiratory failure (measured at the end of the successful spontaneous breathing trial) was determined. The receiving operating characteristic curve showed a cutoff value for lung ultrasound score > 14 estimated by maximizing the Youden index with an area under the curve of 0.8667.

Randomisation and trial intervention

In patients who successfully passed a SBT, randomisation was performed before extubation following the LUS assessment. Patients were randomly assigned (1:1 ratio) to the LUS intervention group or to the control group. Randomisation was performed centrally through a dedicated, password-protected web-based system, using computer-generated permuted blocks. Within each block, the number of participants allocated to each of the two treatment arms was equal. In the LUS intervention group, the LUS was communicated to the attending physician. Patients with LUS ≥ 14 received prophylactic 2 h HFNO alternating with 1 h NIV during two days whereas patients with LUS < 14 received conventional oxygen. In the control group, the LUS was not communicated to the attending physician and patients received conventional oxygen.

HFNO was delivered using large bore binasal silicon prongs through a heated humidifier (MR850, Fisher & Paykel Healthcare®, Auckland New Zealand). A high flow ranging between 50 and 60 L/min was delivered to meet patient's comfort. The patient was asked to breathe through the nose with the mouth closed to generate a positive end-expiratory pressure. NIV was delivered through a face mask connected to a ventilator equipped with a MR850 humidifier and providing a pressure support ranging between 5 and 10 cmH_2O to obtain a tidal volume of 7–10 ml kg^{-1} of predicted body weight. The fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure level were adjusted to maintain a peripheral capillary oxygen saturation (SpO_2) ≥ 92%. Conventional oxygen was delivered by a non-rebreathing face mask using an oxygen flow rate ranging from 10 to 15 L min^{-1} (mean FiO_2 0.37 ± 0.2). In both groups, PRF, defined by predetermined criteria (*see* additional file 2, pages 15, 67 and 84), was treated by rescue NIV and/or reintubation.

Clinical tolerance, respiratory discomfort and serious adverse events were prospectively assessed and compared between the three modes of respiratory support (*see* additional file 2, p 86).

Outcomes

The primary outcome was the incidence of PRF within the 48 h following extubation in patients with LUS ≥ 14.

PRF was defined by the occurrence of 2 among the following signs: 1—increase of oxygen flow as O_2 mask > 9 L/min to maintain SpO_2 > 90% 2—respiratory rate > 30 breaths/min with activation of accessory inspiratory muscles, fatigue, respiratory arrest, major bronchial

obstruction 3—hypercapnia > 50 mmHg with pH < 7.35 4—poor hemodynamic tolerance of respiratory origin, heart rate > 120 beats/min, systolic blood pressure > 200 or < 90 mmHg, cardiac arrhythmias, cardiac arrest for respiratory cause 5—poor neurological tolerance of respiratory origin with hypoxic or hypercapnic encephalopathy, agitation, loss of consciousness, confusion, coma, convulsions.

For patients of the LUS intervention group receiving prophylactic NIV + HFNO, PRF was treated by rescue NIV, defined by the increased duration in NIV sessions beyond 8 h per day and the increase in positive end-expiratory pressure to meet oxygen requirements. For patients of the control group, PRF was treated by rescue NIV and/or HFNO. In both groups, death occurring within 48 h following extubation was classified as PRF.

Secondary outcomes were the incidence of PRF and reintubation within the first 7 days following extubation, number of ventilator-free days at day 28 (non-survivors were assigned to have zero ventilator-free day), length of stay in the ICU and mortality in the ICU at day 28 and 90. In both groups, death occurring within 7 days after extubation was classified as PRF.

Sample size estimation

Using estimates derived from previous data [16], we anticipated that 85% of patients would successfully pass the SBT and that the incidence of PRF in patients with a LUS ≥ 14 would be approximately 65%. We determined that 192 patients would need to be enrolled to provide the trial with 80% power to detect a 30% relative reduction of PRF, at a two-tailed alpha level of 0·05. To account for an incidence of 40% of patients with a LUS ≥ 14 in a similar patient population [16], and a possible incidence of laryngospasm, emergency surgery and cross-over of 10% of patients, enrolment of 650 extubated patients was planned.

Statistical analysis

The coordinating centre, the statistician and all the investigators remained unaware of the trial-group assignments until the end of the study where data were locked. The trial protocol and statistical analysis plan were evaluated and approved by independant reviewers of the French Ministry of Health when the WIN-IN-WEAN study was submitted for funding to the "Programme Hospitalier de Recherche Clinique Regional 2014" (University Hospital of Poitiers, France PHRCI-14-003).

All statistical analyses were performed in the modified intention-to-treat population, which was prespecified as all randomised patients without those who had to be reintubated after randomisation for laryngospasm or intercurrent surgery. In the modified intention-to-treat population, patients with major protocol violations (patients randomised after mechanical ventilation < 48 h, control patients treated by NIV and/or HFNO, control patients treated by NIV and/or HFNO and LUS intervention patients treated by conventional oxygen) were included in the statistical analysis. For the primary analysis, unavailable data were attributed the worst value of the effect of treatment (maximum bias). In patients with early withdrawal from the study, the number of ICU ventilator-free days at the end of the study were considered. For the analysis of the length of ICU stay and mortality, patients lost for follow up were censored.

The primary outcome was compared between the two groups using an unadjusted chi-square test. Other binary outcomes were tested using an unadjusted chi-square test or Fisher's exact test as appropriate. Results are reported as relative risks with 95% confidence intervals. Adjusted analyses were performed with the use of robust random-effect Poisson generalised linear mixed model regression with robust variance for binary outcomes [29] and linear mixed regression for continuous outcomes, with study site as a random effect. Prespecified covariates were fixed according to clinical relevance. Multicollinearity between variables was assessed by computing the variance inflation factor and using the Farrar–Glauber test. The Akaike information criterion and Bayesian information criterion were calculated and used as model diagnostics to determine how well the model fit improved following addition of covariates. Time-to-event was compared between the two groups using the Kaplan–Meier method. A marginal Cox proportional-hazards model was used to estimate the hazard ratio and 95% confidence interval. The proportional hazard hypothesis was evaluated using the Schoenfeld test and plotting residuals.

No correction for multiple testing was applied in the analyses of secondary outcomes. Complete case analysis was performed for all outcomes. We did not compensate for dropouts. The effects of LUS ≥ 14 and < 14 on outcomes were compared in patients treated by conventional oxygenation using an unadjusted Fisher's exact test. A two-sided p value of less than 0.05 was considered to indicate statistical significance. All analyses were generated with the use of Stata software, version 15.0 (StataCorp).

Results

Patients

From March 1st, 2014 through May 31, 2018, 1496 patients were eligible for inclusion in the study. 664 underwent randomisation, 333 in the LUS intervention group and 331 in the control group (Fig. 1). Two hundred and forty patients had a LUS ≥ 14, 134 in the LUS intervention group and 106 in the control group. After

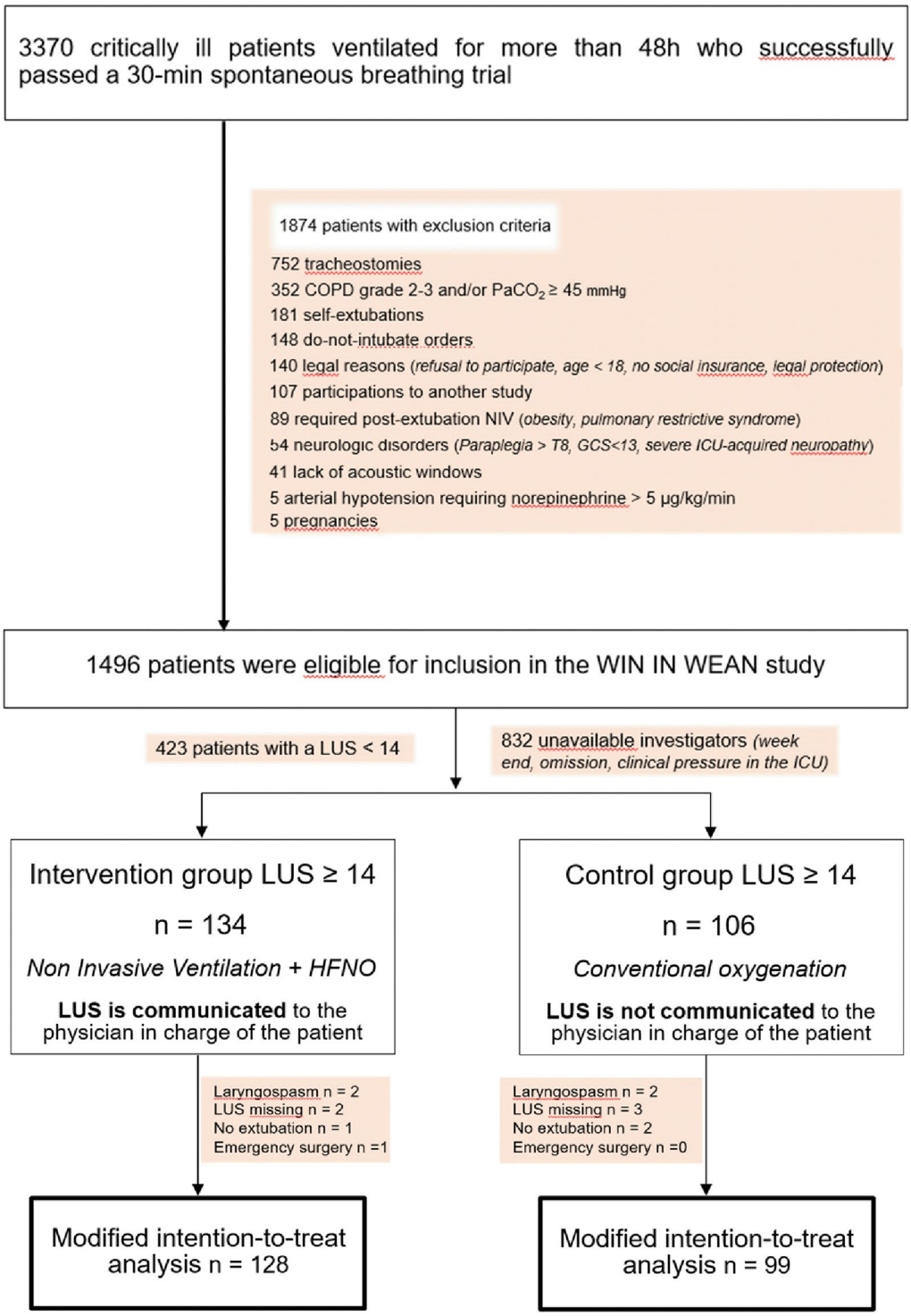

Fig. 1 Profile of the WIN-IN-WEAN trial. In the control group, the LUS performed at the end of the spontaneous breathing trial was not communicated to the physician and patients received conventional oxygen after extubation. In the LUS intervention group, the LUS was communicated to the physician and high-risk patients (LUS ≥ 14) received NIV alternating with HFNO whereas low-risk patients (LUS < 14) received conventional oxygen. After randomisation, 230 patients had a LUS ≥ 14 and 424 a LUS < 14. After exclusion of patients in whom LUS was missing, who were not extubated or reintubated for laryngospasm and emergency surgery, the main objective was assessed in 227 patients with LUS ≥ 14, 99 in the control group and 128 in the intervention group (modified intention-to-treat analysis). *LUS* lung ultrasound score; *COPD* chronic obstructive pulmonary disease; *NIV* noninvasive ventilation; *GCS* Glasgow coma score; *ICU* Intensive Care Unit; *HFNO* high-flow nasal oxygen

exclusion of patients who were not extubated, who had to be reintubated for nonrespiratory reasons and those whose LUS was missing, 227 patients with LUS ≥ 14 were analyzed, 128 in the LUS intervention group and 99 in the control group. The characteristics of the patients are shown in Table 1. Five hundred and eleven patients received conventional oxygen following extubation. The incidence of PRF was significantly lower in the 412 patients with LUS < 14 compared to the 99 patients with LUS ≥ 14: 12.8% vs 28.3% at day 2, $p < 0.001$ and 18.7% vs 38.4% at day 7, $p < 0.001$. This result confirms that the LUS measured at the end of the SBT is highly predictive of PRF.

Primary outcome and treatment of postextubation respiratory failure

In the modified intention-to-treat population, the main objective of the study was met (Table 2 and Fig. 2): in patients with LUS ≥ 14, the 2-day prophylactic NIV alternating with HFNO (mean $FiO_2 = 0.39 \pm 14$) significantly reduced the incidence of PRF within 48 h (28% vs 19%, $p = 0.01$).

In both groups, rescue NIV was implemented as a treatment of PRF. Hypercapnic PRF ($PaCO_2 \geq$ than 45 mmHg) was present in 71% of control patients and in 81% of LUS intervention patients ($p = 0.32$). Rescue NIV allowed to avoid reintubation of 44% of the control patients who developed PRF while on conventional oxygen and of 12% of the LUS intervention patients who developed PRF while on prophylactic NIV + HFNO ($p = 0.008$).

Secondary outcomes

A single secondary objective was met: the 2-day prophylactic NIV alternating with HFNO significantly reduced the incidence of PRF at day 7 (38% vs 30%, $p = 0.02$). Reintubation rate, mortality, duration of mechanical ventilation, and duration of ICU stay were not reduced by prophylactic NIV alternating with HFNO.

Adverse events

Conventional oxygen, HFNO and NIV were well tolerated with a moderate respiratory discomfort. There was no significant difference among the groups in the incidence of serious adverse events. Two control patients died before Day 2 and 8 before Day 7. In the LUS

Table 1 Clinical characteristics of patients with a LUS ≥ 14 measured at the end of the spontaneous breathing trial

Characteristics	Noninvasive ventilation + high-flow nasal oxygen (n= 128)	Conventional oxygen (n= 99)	*p*
At the time of admission to the ICU			
Age	64.9 ± 14.6	62.8 ± 16.5	0.31
Age > 65 (%)	68 (53)	47 (47)	0.40
Sex (male, %)	90 (70)	66 (67)	0.56
SAPS II	49.4 ± 16.8	51 ± 17.5	0.56
SOFA	9.8 ± 4.4	10.2 ± 4.4	0.50
Pre-existing cardiovascular disease (%)	23 (18)	15 (15)	0.57
Pre-existing respiratory disease (%)	9 (7)	5 (5)	0.52
LVEF < 50%	11 (9)	8 (8)	0.89
Cause of admission			0.62
Medical (%)	83 (65)	61 (61)	
Surgical (%)	33 (26)	30 (30)	
Multiple trauma (%)	12 (9)	8 (8)	
At inclusion in WIN-IN-WEAN			
Lung ultrasound score	17.5 ± 3.1	17.9 ± 3.3	0.36
ΔWeight from admission to inclusion (kg)	2.0 [0–5]	4.5 [0.3–7.3]	0.008
Pleural effusion (%)	17 (13)	12 (12)	0.84
Pleural drainage before extubation (%)	15 (88)	10 (83)	> 0.99
Duration of mechanical ventilation (days)	8 [4–10]	7 [4–7]	0.09
Duration of replacement renal therapy (days)	4 [2–6] n = 35	5 [2–6] n = 27	0.88
Time in the ICU since admission (days)	7 [4–9]	6 [4–8]	0.20
Vasopressor administration (days)	4 [2–5] n = 112	4 [2–5] n = 82	0.92

Patients who had emergency surgery (n = 1) or were reintubated for laryngospasm (n = 4) after extubation were excluded from the analysis. Quantitative variables are expressed as mean ± SD or median interquartiles [p 25–p 75]. *LUS* lung ultrasound score; *LVEF* left ventricular ejection fraction; *SAPS* simplified acute physiology score; *SOFA* Sequential Organ Failure assessment; *ICU* Intensive Care Unit

Table 2 Primary and secondary outcomes in high-risk patients (LUS ≥ 14 measured at the end of the spontaneous breathing trial)

Outcome	Noninvasive ventilation + High flow nasal oxygen n = 128	Conventional oxygen n = 99	*p*	Relative risk (95 CI) (Noninvasive ventilation + high flow nasal oxygen)
Extubation failure 48 h (%)**	19 (14.8)	28 (28.3)	0.01	0.52 (0.31 to 0.88)
Extubation failure Day 7 (%)**	30 (23.8) n = 126	38 (38.4) n = 99	0.02	0.62 (0.44 to 0.96)
Reintubation 48 h (%)	17 (13.3)	16 (16.2)	0.54	0.82 (0.44 to 1.54)
Reintubation Day 7 (%)	28 (22.2) n = 126	24 (24.2) n = 99	0.72	0.92 (0.57 to 1.48)
MV after extubation (days)	6 [4–13] n = 27	9 [4–24] n = 26	0.17	−0.31 (−0.76 to 0.13)*
Total ICU stay (days)	13 [8–20] n = 126	15 [8–23] n = 99	0.18	−0.11 (−0.27 to 0.05)*
ICU stay from inclusion (days)	5 [3–10]	6 [3–13]	0.11	−0.18 (−0.40 to 0.04) *
ICU mortality (%)	9 (7.0)	10 (10.1)	0.41	0.70 (0.29 to 11.65)
Hospital mortality (%)	23 (18.1) n = 127	18 (18.2) n = 99	0.99	1 (0.57 to 1.74)
Mortality day 28 (%)	20 (16.0) n = 125	11 (11.2) n = 98	0.31	1.43 (0.72 to 2.83)
Mortality day 90 (%)	27 (22.3) n = 121	9 (19.6) n = 97	0.63	1.14 (0.68 to 1.92)

Patients who had to undergo emergency surgery (n = 1) and who were reintubated for laryngospasm (n = 4) after randomisation were excluded from the analysis. Therefore, 138 patients were analyzed in the intervention group and 99 in the control group (modified intention to treat analysis). In the control group, the LUS was not communicated to the physician and patients received conventional oxygen after extubation. In the LUS intervention group, the LUS was communicated to the physician and patients received prophylactic noninvasive ventilation alternating with High Flow Nasal Oxygen). Low-risk patients (LUS < 14) received conventional oxygen. Qualitative variables are expressed as percentage (%) and quantitative variables as median values and interquartiles [p 25–p 75]. MV = Mechanical ventilation; *LUS* lung ultrasound score; *ICU* Intensive Care Unit. *standardized mean difference, incremented per log unit. **Extubation failure was defined by the occurrence of postextubation respiratory failure, reintubation or death

intervention group, no patient died before Day 2 and five died before Day 7.

Discussion

In high-risk patients whose PRF risk was defined as a LUS ≥ 14 at the end of the SBT, a two-day prophylactic HFNO alternating with NIV, reduced the rate of PRF at day 2 and 7, compared to the administration of conventional oxygen. Reintubation, duration of mechanical ventilation, length of ICU stay and mortality were not reduced. Compared to previous Randomised controlled trials performed in high-risk patients [9, 12–14], the WIN IN WEAN randomised controlled trial has two originalities: first it identifies the personal risk at the time of extubation using bedside lung ultrasound and second, patients with COPD were excluded. The number of included patients allowed to meet the objectives of the Randomised controlled trial (see additional file 4).

Prophylactic NIV alternating with HFNO prevented PRF but failed to reduce reintubation. More than 70% of the patients with PRF were hypercapnic and treated by rescue NIV to avoid reintubation. Reintubation was avoided in 44% of hypercapnic PRF occurring in patients under conventional oxygen and only in 12% of hypercapnic PRF occurring in patients under prophylactic NIV alternating with HFNO. This result challenges the classical recommendation that rescue NIV should not be used to treat PRF [19]. This conditional recommendation, made by European and American respiratory societies in 2017, was based on a RCT published in 2004 suggesting that rescue NIV could delay reintubation and increase mortality in hypercapnic patients with PRF [30]. However, a post-hoc analysis of a recent RCT reported that rescue NIV avoided reintubation in 44% of patients with PRF [5], a result similar to ours. The very high proportion of hypercapnic PRF suggests that a LUS ≥ 14 identifies patients with a severe deterioration of their respiratory function. In the PULCO study [16], patients with a LUS of 17, a score similar to the median score observed in high-risk patients of the present study, had an incidence of postextubation respiratory failure of 85%. Five randomised controlled rials have examined the best oxygen and respiratory support to prevent PRF and avoid reintubation [9, 11–14]. Three were performed in high-risk patients [9, 12, 13], and one in very high-risk patients (≥ 4 risk factors) [14]. The present study differs from these studies in two ways: the high risk of PRF was individually assessed by measuring the LUS at the end of a successful

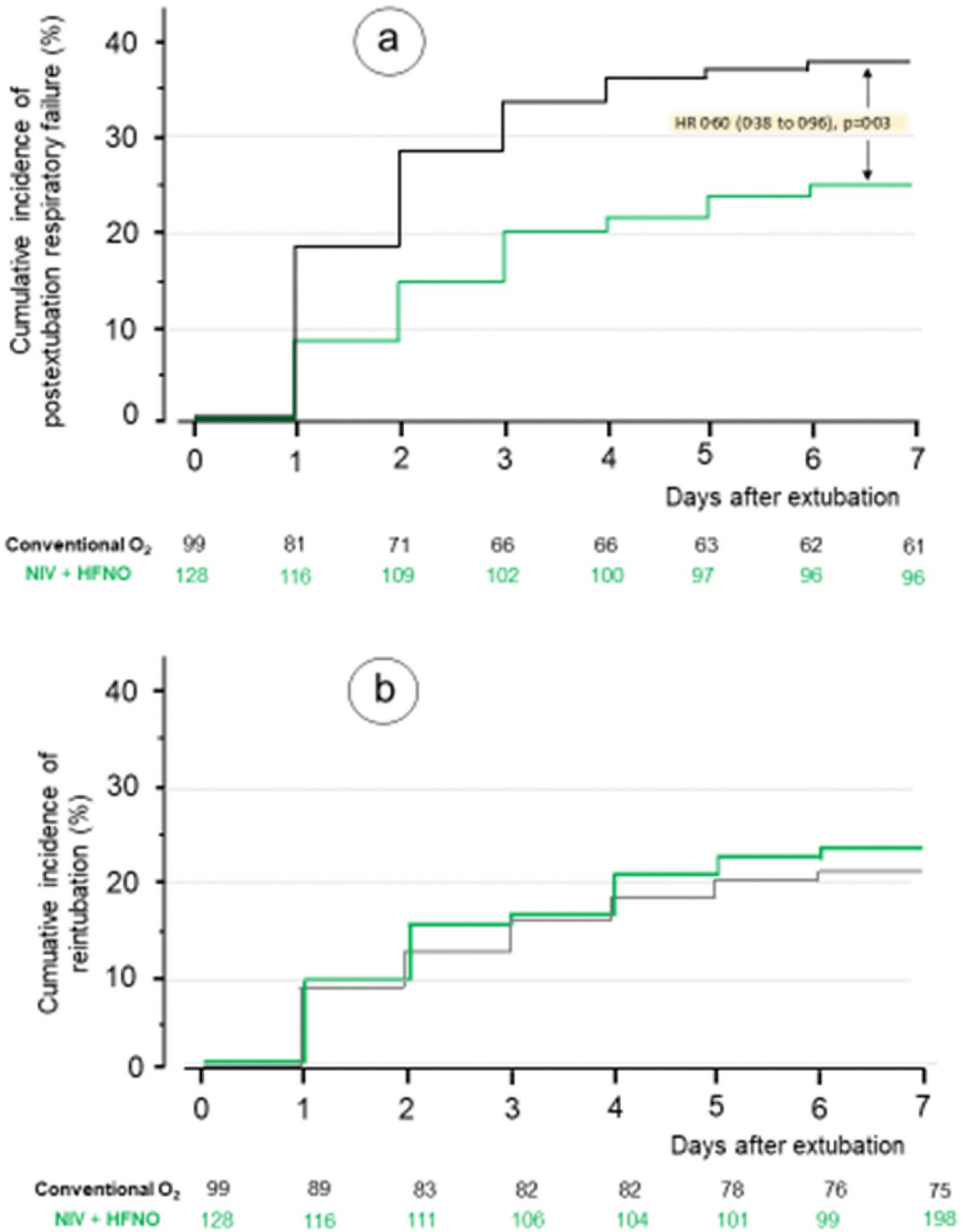
a
Cumulative incidence of postextubation respiratory failure (%)
40
30
20
10
0
HR 0·60 (0·38 to 0·96), p=0·03
0 1 2 3 4 5 6 7
Days after extubation
Conventional O2 99 81 71 66 66 63 62 61
NIV + HFNO 128 116 109 102 100 97 96 96
b
Cumulative incidence of reintubation (%)
40
30
20
10
0
0 1 2 3 4 5 6 7
Days after extubation
Conventional O2 99 89 83 82 82 78 76 75
NIV + HFNO 128 116 111 106 104 101 99 198

Fig. 2 Kaplan–Meier analysis of time from extubation to postextubation respiratory failure (**a**) and Reintubation (**b**). Black line = 99 patients with LUS ≥ 14 treated by conventional oxygen after extubation; Green line = 128 patients with LUS ≥ 14 treated by prophylactic HFNO alternating with NIV after extubation. *LUS* lung ultrasound score; *HFNO* high-flow nasal oxygen

SBT, and patients with COPD were excluded. This exclusion criteria allowed administration of conventional oxygen in the control group, an oxygen support inadvisable for patients with COPD [14–16]. In patients with COPD, prophylactic NIV is equivalent to prophylactic HFNO to prevent PRF and reintubation [12], and alternating NIV and HFNO, appears superior to NIV alone [9].

The administration of prophylactic NIV alternating with HFNO following extubation, did not modify reintubation rate, mortality, duration of mechanical ventilation and length of stay in the ICU. In other words, a 2-day administration of prophylactic NIV alternating with HFNO did not show any benefit on long term outcome. From a resource utilisation standpoint,

prophylactic NIV alternating with HFNO was more demanding and costly than conventional oxygen with rescue NIV to achieve same clinical outcome. The possible reasons why outcomes were not changed are to be discussed. A higher incidence of postextubation cardiac failure and incompletely treated ventilator-associated pneumonia in the LUS intervention group is unlikely. In the WIN IN WEAN study, therapeutic optimisation was systematically performed before extubation: drainage of pleural effusions > 500 ml, reduction of fluid overload, bronchoscopic suctioning of bronchial plugs, and distal pulmonary sampling for diagnosis of persisting ventilator-associated pneumonia. Pre-existing cardiovascular disease and cardiac dysfunction (left ventricular ejection fraction < 50%) were similar in both groups at the time of inclusion. A greater respiratory muscle weakness in the intervention group cannot be ruled out as diaphragm ultrasound was not performed in the WIN IN WEAN study. Further prospective studies are warranted to determine the role of respiratory muscle weakness in PRF occuring 7 days after extubation, a muscle dysfunction that would indicate a prolonged use of prophylactic NIV combined to HFNO. The most likely reason why duration of mechanical ventilation and mortality were not reduced in the intervention group, is that rescue NIV was as efficient as prophylactic NIV alternating with HFNO to treat postextubation respiratory failure.

The present study has originality, strengths and limitations. A LUS > 14 was found highly predictive of PRF and reintubation, confirming our previous findings in a larger series of patients [16]. LUS is correlated with the extend of lung aeration loss [20, 26, 31]. It does not indicate the mechanism involved, respiratory muscle dysfunction, interstitial or pulmonary edema, or consolidation and atelectasis. A LUS ≥ 14 indicates the presence of a severe lung aeration defect and doubles the risk of PRF at day 7. Therefore the high-risk of PRF was personalised and did not hinge on classical clinical criteria that are unable to predict the individual risk at the time of extubation. The pivotal role of lung ultrasound in guiding the weaning process and improving individual outcome will be reported in a second article, centered on LUS for predicting PRF. In the control group, patients with a LUS ≥ 14 (high risk of PRF) were not identified by the physician in charge, thereby avoiding therapeuthic bias that could have modify the outcome. PRF and reintubation were assessed over 7 days following extubation. Patients with COPD were excluded providing the possibility of using conventional oxygen in patients with a LUS ≥ 14. An important limitation is that conventional oxygen was not compared with prophylactic NIV or HFNO in low-risk patients (LUS < 14), where a prophylactic 24 h-HFNO may significantly reduce PRF and reintubation [11]. The efficacy of rescue NIV to prevent reintubation in patients of the LUS intervention group was analysed a posteriori.

In conclusion, prophylactic NIV alternating with HFNO reduces PRF compared to conventional oxygen without reducing reintubation, mortality and length of ICU stay in critically ill patients at high individual risk of PRF and free of COPD. Rescue NIV may avoid reintubation when PRF occurs in patients on conventional oxygen and is less efficient when PRF occurs in patients on prophylactic NIV and HFNO. From a resource utilisation standpoint, prophylactic NIV alternating with HFNO was more demanding and costly than conventional oxygen with rescue NIV to achieve same clinical outcome. A future RCT is warranted to know whether the results of the WIN IN WEAN study are valid in a population of COPD patients undergoing weaning from mechanical ventilation, and whose high-risk will be determined by a lung ultrasound score ≥ 14.

Abbreviations

COPD	Chronic obstructive pulmonary disease
PRF	Postextubation respiratory failure
FiO_2	Fraction of inspired oxygen
HFNO	High-flow nasal oxygen
ICU	Intensive Care Unit
LUS	Lung ultrasound score
NIV	NonInvasive ventilation
$PaCO_2$	Partial pressure of arterial carbon dioxide
SBT	Spontaneous breathing trial
SpO_2	Peripheral capillary oxygen saturation

Supplementary Information

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Additional file1.

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Author contributions

J-J. Rouby and S. Perbet conceived and designed the study. Draft of the article including tables, figures and online supplement was prepared by J-J; Rouby. Chinese centers were selected, trained and enrolled in the WIN-IN-WEAN study by J-J. Rouby who wrote the English version of the amended protocol. J. Lyu, X. Jing, and M. Zhang were trained for lung ultrasound in the Multidisciplinary ICU of La Pitié-Salpêtrière in Paris. Y.Gao and other investigators of the Emergency Department of the 2nd affiliated hospital of Hangzhou were trained to lung ultrasound by H. Brisson in 2013 during a 2-month period. S. Perbet applied for the Programme Hospitalier de Recherche Clinique Interrégional 2014 of the French Ministry of Health PHRCI-14-00, submitted the Amendement to the protocol on October 2015 and wrote the French version of the amended protocol. The Biostatistics Unit of the Direction of Clinical Research and Innovation (CHU Clermont-Ferrand, Clermont-Ferrand, France) supervised data collection and accuracy of redcap filling by French and Chinese centres and performed data analysis. Adequate filling of redcap files in France and China was followed up by D. Morand. Adequacy between rough and redcap data was verified in each French center by D. Morand and in each Chinese center by the principal investigator (M. Zhang, J. Lyu and X. Jing). J-J. Rouby, S. Pereira and D. Morand had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data analysis was performed by J-J. Rouby, A. Monsel, J-M. Constantin, X. Jing, D; Morand and B. Pereira during two research meetings held in Clermont-Ferrand in 2018 and in Paris in 2021. Statistical analysis was performed by B. Pereira. Adequacy between redcap data and data provided in the article were verified by J-J. Rouby, D. Morand and B. Pereira during two research meetings held in September 2022. E. Futier, J-M. Constantin, A. Monsel, J-P. Quenot, M. Assefi, X. Jing, P. Guerci, L. Puybasset, C. Arbelot and L. Malbouisson provided crucial revision for important intellectual content and gave final approval of the manuscript. J-J. Rouby had final responsibility for the decision to submit for publication. All other authors participated to daily patients' screening for establishing the flow chart, patients' inclusion, red, reviewed and approved the manuscript. Data collected for the study, including individual participant data, data dictionary defining each field in the set, and study protocol were made available to others.

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Availability of data and materials

Data will be communicated as de-identified participant data according to French law, and will be available after publication of the manuscript. Data are stored at the Direction de la Recherche Clinique, University Hospital of Clermont-Ferrand, Clermont-Ferrand, France. Data requests should be address to Dr Bruno Pereira (bpereira@chu-clermontferrand.fr) who will send the data after receipt of a signed data access agreement. The proposed use of the data and analyses must be approved by the Scientific Committee.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee Sud-Est VI of Clermont-Ferrand, France and by the local Ethics Committee of each Chinese centre. The WIN-IN-WEAN study was registered at ClinicalTrials.gov with identifier number 1 NCT02123940.

Consent for publication

Not applicable.

Competing interests

J-M. Constantin reports personal fees and non-financial support from Drager, GE Healthcare, Sedana Medical, Baxter, and Amomed; personal fees from Fisher and Paykel Healthcare, Orion, Philips Medical, and Fresenius Medical Care; and non-financial support from LFB and Bird Corporation, outside of the submitted work. All other authors declare that they have no competing interests.

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References

1. Tobin MJ, Jubran A. Weaning from mechanical ventilation. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. 2nd ed. New York: McGraw-Hill Medical Publishing Division; 2006. p. 1185–220.
2. Tobin MJ, Laghi F. Extubation. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. 2nd ed. New York: McGraw-Hill Medical Publishing Division; 2006. p. 1221–37.
3. Béduneau G, Pham T, Schortgen F, Piquilloud L, Zogheib E, Jonas M, et al. Epidemiology of weaning outcome according to a new definition. The WIND study. Am J Respir Crit Care Med. 2017;195(6):772–83.
4. Thille AW, Richard JC, Brochard L. The decision to extubate in the intensive care unit. Am J Respir Crit Care Med. 2013;187(12):1294–302.
5. Thille AW, Monseau G, Coudroy R, Nay MA, Gacouin A, Decavèle M, et al. HIGH-WEAN Study Group and the REVA Research Network. Non-invasive ventilation versus high-flow nasal oxygen for postextubation respiratory

failure in ICU: a post-hoc analysis of a randomized clinical trial. Crit Care 2021;25(1):221.
6. Torres A, Gatell JM, Aznar E, El-Ebiary M, Puig de la Bellacasa J, González J, et al. Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. Am J Respir Crit Care Med. 1995;152(1):137–41.
7. Frutos-Vivar F, Esteban A, Apezteguia C, González M, Arabi Y, Restrepo MI, et al. Outcome of reintubated patients after scheduled extubation. J Crit Care. 2011;26(5):502–9.
8. Schmidt GA, Girard TD, Kress JP, Morris PE, Ouellette DR, Alhazzani W, et al. ATS/CHEST Ad Hoc Committee on Liberation from Mechanical Ventilation in Adults. Official Executive summary of an American thoracic society/American College of Chest Physicians Clinical Practice Guideline: liberation from mechanical ventilation in critically ill adults. Am J Respir Crit Care Med 2017;195(1):115–9.
9. Thille AW, Muller G, Gacouin A, Coudroy R, Decavèle M, Sonneville R, et al. HIGH-WEAN Study Group and the REVA research network. Effect of postextubation high-flow nasal oxygen with noninvasive ventilation vs high-flow nasal oxygen alone on reintubation among patients at high risk of extubation failure: a randomized clinical trial. JAMA. 2019;322(15):1465–75.
10. Fernando SM, Tran A, Sadeghirad B, Burns KEA, Fan E, Brodie D, Munshi L, et al. Noninvasive respiratory support following extubation in critically ill adults: a systematic review and network meta-analysis. Int Care Med. 2022;48(2):137–47.
11. Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialp G, et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. JAMA. 2016;315(13):1354–61.
12. Hernández G, Vaquero C, Colinas L, Cuena R, González P, Canabal A, et al. Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. JAMA. 2016;316(15):1565–74.
13. Fernandez R, Subira C, Frutos-Vivar F, Rialp G, Laborda C, Masclans JR, et al. High-flow nasal cannula to prevent postextubation respiratory failure in high-risk non-hypercapnic patients: a randomized multicenter trial. Ann Int Care. 2017;7(1):47.
14. Hernández G, Paredes I, Moran F, Buj M, Colinas L, Rodríguez ML, et al. Effect of postextubation noninvasive ventilation with active humidification vs high-flow nasal cannula on reintubation in patients at very high risk for extubation failure: a randomized trial. Int Care Med. 2022;48(12):1751–9.
15. Maggiore SM, Battilana M, Serano L, Petrini F. Ventilatory support after extubation in critically ill patients. Lancet Resp Med. 2018;6(12):948–62.
16. Soummer A, Perbet S, Brisson H, Arbelot C, Constantin JM, Lu Q, et al. Ultrasound assessment of lung aeration loss during a successful weaning trial predicts postextubation distress. Crit Care Med. 2012;40(7):2064–72.
17. Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33(11):2465–70.
18. Thille AW, Boissier F, Ben-Ghezala H, Razazi K, Mekontso-Dessap A, Brun-Buisson C, et al. Easily identified at-risk patients for extubation failure may benefit from noninvasive ventilation: a prospective before–after study. Crit Care. 2016;20:48.
19. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426.
20. Bouhemad B, Liu ZH, Arbelot C, Zhang M, Ferarri F, Le-Guen M, et al. Ultrasound assessment of antibiotic-induced pulmonary reaeration in ventilator-associated pneumonia. Crit Care Med. 2010;38(1):84–92.
21. Thille AW, Gacouin A, Coudroy R, Ehrmann S, Quenot JP, Nay MA, et al. REVA Research Network. Spontaneous-breathing trials with pressure-support ventilation or a T-Piece. N Engl J Med 2022;387(20):1843–54.
22. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. Eur Respir J. 2007;29(5):1033–56.
23. Roch A, Bojan M, Michelet P, Romain F, Bregeon F, Papazian L, et al. Usefulness of ultrasonography in predicting pleural effusions > 500 ml in patients receiving mechanical ventilation. Chest. 2005;127(1):224–32.
24. Remérand F, Dellamonica J, Mao Z, Ferrari F, Bouhemad B, Jianxin Y, et al. Multiplane ultrasound approach to quantify pleural effusion at the bedside. Int Care Med. 2010;36(4):656–64.
25. Arbelot C, Dexheimer Neto FL, Gao Y, Brisson H, Chunyao W, Lv J, et al. APECHO Study Group. Lung ultrasound in emergency and critically ill patients: number of supervised exams to reach basic competence. Anesthesiology 2020;132(4):899–907.
26. Caltabeloti F, Monsel A, Arbelot C, Brisson H, Lu Q, Gu WJ, et al. Early fluid loading in acute respiratory distress syndrome with septic shock deteriorates lung aeration without impairing arterial oxygenation: a lung ultrasound observational study. Crit Care. 2014;18(3):R91.
27. Mongodi S, Bouhemad B, Orlando A, Stella A, Tavazzi G, Via G, et al. Modified lung ultrasound score for assessing and monitoring pulmonary aeration. Ultraschall Med. 2017;38(5):530–7.
28. Rouby JJ, Arbelot C, Gao Y, Zhang M, Lv J, An Y, et al; APECHO Study Group. Training for lung ultrasound score measurement in critically ill patients. Am J Respir Crit Care Med 2018;198(3):398–401.
29. Plan EL, Maloney A, Trocóniz IF, Karlsson MO. Performance in population models for count data, part I: maximum likelihood approximations. J Pharmacokinet Pharmacodyn. 2009;36(4):353–66.
30. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguía C, González M, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004;350(24):2452–60.
31. Bouhemad B, Brisson H, Le-Guen M, Arbelot C, Lu Q, Rouby JJ. Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. Am J Respir Crit Care Med. 2011;183(3):341–7.

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